Diverse characteristics of addiction necessitate multiple preclinical models

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Diverse characteristics of addiction necessitate multiple preclinical models

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There is an urgent need for the development of treatments and preventative therapies for opioid use disorder. Approximately 27 million people worldwide suffer from an opioid use disorder, with the majority of people misusing heroin (1). In 2015, it was globally estimated that 118,000 deaths were attributed directly to opioid use, and overdoses accounted for up to half of these deaths (1). Beyond the risk of overdosing, unsafe drug injection techniques pose another threat to opioid users – the spread of virally-transmitted diseases. This commentary, which will highlight the work of Venniro *et al.* published in this issue of Biological Psychiatry (2), argues that a multi-model research approach should be used to enhance our understanding of addiction and develop therapies.

Across individuals, a combination of factors contributes to the development and escalation of drug use. Accordingly, personalized delivery of both biomedical and psychosocial treatments may have the most significant impact for the individual who is either trying to achieve abstinence or lessen potential addiction-related harms. Biomedical interventions for opioid use disorder may involve transferring the individual onto another, safer drug. Methadone and buprenorphine, for example, are sometimes used as substitution treatments for heroin addiction. While these replacement drugs might not bring about the same magnitude of desired effects as heroin, their use mitigates withdrawal symptoms. Furthermore, oral administration of these replacement drugs is safer than the injection of heroin.

Psychosocial treatments for opioid use disorder can take many forms, ranging from forced court-ordered programs to voluntary cognitive and behavioral therapies. For example, in the United States, Hawaii's Opportunity Probation with Enforcement program puts drug-possession arrestees on probation and subjects them to random or scheduled drug tests. Failure to pass these tests results in short and predictable periods of incarceration, and this threat is believed to motivate abstinence. In contrast to strategies that combat addiction that involve punishment, contingency management therapies offer incentives or rewards (e.g., vouchers) to substance misusers for meeting specific behavioral goals (3). Similarly, community reinforcement programs provide a social reward (e.g., access to work, friends,

family) that is contingent upon stopping drug-use (4). Despite the achievements of these reward-based programs, they are expensive to run, abstinence success rates often diminish over time, and the danger of relapsing into drug misuse remains when the program ends (3, 5). Regardless, the initial recovery observed during psychosocial programs highlights how individuals with a substance use disorder might be able to adapt their behavior to reduce drug-seeking and -taking. Furthermore, by combining biomedical and psychosocial therapies, long-term abstinence may be achievable.

The magnitude of the opioid use crisis necessitates the development of preventative measures and new treatment options for the addiction. Much of our knowledge on how drug use impacts the brain is based on the study of preclinical animal models. In such experiments, the neurobiology of addiction is assessed in rodents (e.g., rats) that are placed in chambers and trained to perform an action (e.g., press a lever) to take a drug of abuse (e.g., heroin or cocaine). Unfortunately, scientific attempts to translate knowledge gained from these rodent studies to improve the human condition have been limited in their success. Perhaps one reason for this problem is that self-administration studies in rodents often do not consider psychosocial factors influencing addiction; it is essential to account for psychosocial features in animal models because such factors aid recovery in humans (3, 4).

Translational medical research uses the knowledge gained from basic and preclinical studies to develop new therapies to treat disorders in people (a ‘bench to bedside’ approach). Reverse-translational research starts in the opposite direction: knowledge of how to effectively treat medical conditions in people (based on observation, experimentation, clinician expertise) informs the development of basic and preclinical research projects (Figure 1). Objectives of reverse-translational research include understanding why treatments work and refining/improving therapies. Reverse-translational preclinical studies can account for psychosocial influences on addiction development and its treatment, including how giving substance misusers non-drug rewards can reduce their drug-intake (3, 4). An example of such an approach is the rat community reinforcement model developed by Venniro and colleagues (2, 6). In this model, rats are first trained on separate operant tasks;

in distinct sessions, rats learn that by pressing one lever they receive an infusion of a drug reward (e.g., heroin), while pressing a different lever gives them a social reward (e.g., interaction with a familiar rat they have previously lived with). Later, when given a choice to press a lever for heroin or access to their social partner, rats primarily choose their partner over drug – the authors refer to this as 'voluntary abstinence' from the drug (2). Similar findings were also recently observed for methamphetamine (6).

Another issue that Venniro *et al.* investigate is susceptibility to relapse into drug-pursuit after re-exposure to cues (conditioned stimuli) that are predictive of drug availability. Studying how cues can instigate relapse is essential because neurological responsiveness to stimuli may predict relapse susceptibility in people (7). In this issue of Biological Psychiatry, Venniro *et al.* found that, compared to rats that underwent 'forced abstinence' from heroin (similar to going 'cold turkey'), rats that had undergone 'voluntary abstinence' were less likely to 'relapse' into heroin pursuit (2). The ability of social reward choice to decrease 'relapse' was independent of sex. Similarly, the success of contingency management-based therapies appears to not differ by sex (9; other reports, however, suggest differences in *patterns of drug-use* between sexes in animal models and observations of human behavior - more research is needed). Finally, compared to previous articles, 'voluntary abstinence' was more successful at reducing 'relapse' into methamphetamine pursuit than 'relapse' for heroin (2, 6); this finding highlights the need for modeling and developing diverse treatment options across substance use disorders.

In addition to successfully testing a reverse-translational animal model of addiction, Venniro and colleagues should be commended for publishing details on an improvement to their model (2). By doing so, they will enable other researchers to replicate and build upon their findings – hopefully, this can speed the collaborative development of treatments for addiction. The original version of the rat community reinforcement model required the experimenter to physically separate the rodent social partners in the operant chambers between trials during a single testing session (Experiment 1). Experiment 2 of their article removed the need for researcher intervention; an automated sliding door with a barrier was

installed in the operant chambers that enabled the rats to physically interact for a time-limited period (2). The results from Experiment 2 mirrored those of Experiment 1, demonstrating how rats choose to be social instead of taking heroin, and that 'voluntary abstinence' may protect against 'relapse'.

Beyond reverse-translating the success of community reinforcement, other recent preclinical studies have developed representative models of addiction that are based on observations of human behavior. For example, evidence shows that people prefer to consume cocaine outside the home, while they prefer to take heroin *at* home – such findings are also seen in rats (9). Therefore, environmental contexts play pivotal roles in determining drug-choice. Could behavioral therapies perhaps be modeled in rats that alter motivation to consume a certain drug in specific settings?

In another study, we created a preclinical model based on how certain people with a substance use disorder show flexibility and ingenuity when procuring drugs (10). We have argued that such observations of adaptable human behavior suggest that the act of drug-seeking is not necessarily controlled by 'drug-seeking habits'. Accordingly, we found that, despite the need to be flexible in their drug-seeking, rats still developed 'addictive' behaviors. Finally, recent preclinical models of addiction replicate the intermittent binge-like pattern by which people take cocaine (10). We and others have shown that rats who intermittently 'binge' on a drug display exaggerated addiction-like behaviors compared to other animals that have continuous access to the drug. By accurately replicating in rodents how people seek and take drugs, basic research scientists may be better able to develop treatments for addiction.

Addiction is an extremely complex condition that is influenced by numerous biopsychosocial factors, drugs of choice, and patterns of use. For example, Venniro *et al.* demonstrate drug-specific intricacies by showing how social choice prevents methamphetamine craving but only reduces heroin craving (2, 6). Additionally, if a drug is easily accessible to an individual (e.g., for a drug dealer with constant supply), then adaptability during drug-procurement may not be essential and, therefore, drug-seeking may

(to some extent) become controlled by habit. Thus, when trying to develop viable treatment options for addiction, it is critical to acknowledge how unlikely it is for any single preclinical model to capture the complete multi-faceted nature of substance use and misuse across drugs and people. Instead, scientists should accept that a variety of preclinical models of addiction are required to replicate the diverse contributing factors and features of addiction in people. By collaborating (instead of competing) on the design of translational and reverse-translational preclinical models of addiction, we stand a better chance of creating accurate representations of the human condition that can be used to develop treatments for substance use disorders.

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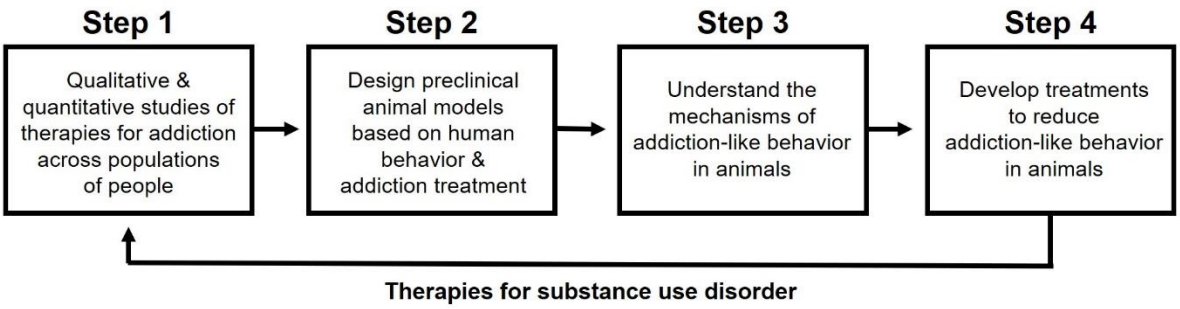
Figures

Figure 1. Reverse-translational strategy for developing substance use disorder treatments. General overview of how both how human observational and experimental studies can inform the design of preclinical models of addiction.


Step 1
Qualitative & quantitative studies of therapies for addiction across populations of people
Step 2
Design preclinical animal models based on human behavior & addiction treatment
Step 3
Understand the mechanisms of addiction-like behavior in animals
Step 4
Develop treatments to reduce addiction-like behavior in animals
Therapies for substance use disorder